## REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are respectfully requested.

By the foregoing amendment, claims 23, 24 and 45 have been canceled without prejudice or disclaimer of the subject matter recited therein. Further, claims 32, 39-42, 44, 46, 48 and 52 have been amended to further clarify Applicants' invention. Support for the amendments can be found throughout the specification. In particular, support for claim 44 can be found in claim 45. In addition, new claims 57-80 have been added. Support for claims 57 and 58 can be found, respectively, on page 19, lines 3-8, and page 18, lines 32-35, of the specification. Support for claims 59-64 can be found in claims 33-38, respectively. Support for claim 65 can be found in originally filed claims 5 and 10. Support for claims 66-71 can be found in originally filed claims 12-17, respectively. Support for claims 72 and 73 can be found in originally filed claims 6 and 2, respectively. Support for claim 74 can be found in originally filed claims 9 and 18. Support for claim 75 can be found in originally filed claim 3. Support for claims 76 and 77 can be found, respectively, on page 19, lines 3-8, and page 18, lines 32-35. Support for claims 78-80 can be found in originally filed claims 21 and 22. Accordingly, no new matter has been added.

## I. Priority

Applicants hereby submit an English language translation of the subject application for the Examiner's consideration.

## II. Claim Objections

Claims 23, 24, 44-46 and 48 have been objected to for informalities. Specifically, claims 23 and 24 have been objected to as being dependent upon a rejected base claim (claim 10).

In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have canceled claims 23 and 24 without prejudice or disclaimer of the subject matter recited therein.

Claim 44 has been objected to for reciting "for At least . . ." in line 2. In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claim 44 to recite "at least" instead of "At least."

Claims 45, 46 and 48 have been objected to for reciting "interleukine." In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have canceled claim 45 and amended claims 46 and 48 to recite "interleukin" instead of "interleukine."

Therefore, Applicants respectfully request withdrawal of the objection of claims 23, 24, 44-46 and 48.

## III. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 32-56 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Examiner has stated that claim 32 is drawn to a recombinant vector encoding at least one early polypeptide and at least one late polypeptide from the papillomavirus, with the exception of a DNA sequence encoding E7 and L2, and claims 39-41, 43, 53 and 54 recite the early polypeptides E6 and/or E7 and L1 and/or L2. Based thereon, the Examiner has concluded that the composition of the dependent claims are contradictory to the independent claim and that it is unclear what Applicants intend.

Independent claim 32 is drawn to a composition comprising one or more recombinant vector(s) genetically engineered to encode at least one early polypeptide and at least one late polypeptide from a papillomavirus, with the exception of the specific combination of DNA sequences coding for the E7 early polypeptide and the L2 late polypeptide. Subsequent claims 39-41, 43, 53 and 54 recite that the early polypeptide is E6 and/or E7 and the late polypeptide is Ll and/or L2.

By definition, dependent claims include all the features of the claims from which they depend and then recite additional features of the claimed invention. Therefore, dependent claims 39-41, 43, 53 and 54 also exclude the E7+L2 combination. For example, claim 39 which is dependent upon claim 32, is directed to a composition

comprising one or more recombinant vector(s) encoding at least one early polypeptide of a papillomavirus selected from E6, E7 or E6 and E7 polypeptide(s) with the exception of the specific combination of DNA sequence coding for the E7 early polypeptide and of DNA sequence coding for the L2 late polypeptide. In other terms, dependent claim 39 covers a composition comprising one or more recombinant vector(s) encoding any combination involving E6 and/or E7 polypeptide(s) and a late polypeptide, such as E6+Ll, E7+Ll, E6+E7+Ll, E6+L2, E6+E7+L2 and E6+E7+Ll+L2. Therefore, dependent claims 39-41, 43, 53 and 54 are not contradictory to independent claim 32.

Furthermore, the Examiner has stated that because the specification does not specifically exclude the E7 and L2 combination, this limitation is new matter. Applicants address this issue below in response to the rejection of claim 32 under 35 U.S.C. § 112, first paragraph.

With respect to the rejection of claims 39 and 41, Applicants submit that the term "native" is used in its usual context, and refers to a polypeptide being identical to the polypeptide encoded by the pepillomavirus genome. However, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claim 39 to recite that the early polypeptide is the E6, E7 or the E6 and E7 polypeptide(s) of a papillomavirus and claim 41 to recite that the late polypeptide is the Ll, L2 or the Ll and L2 polypeptide(s) of a papillomavirus.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 32-56 under 35 U.S.C. § 112, second paragraph.

## IV. Rejections Under 35 U.S.C. § 112, First Paragraph

Claim 32 has been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the invention was filed, had possession of the claimed invention. Specifically, the Examiner has stated that the negative limitation recited in claim 32 (i.e., the exception of the E7 and L2 combination) cannot be found in the original disclosure. Applicants respectfully traverse this rejection.

Applicants submit that in *In re Wright*, 866 F.2d 422 (Fed. Cir. 1989), the Federal Circuit found that exclusionary language (e.g., a provisio) was adequately described in the specification when the specification was read in light of the prior art. It was clear in *In re Wright* that by teaching certain characteristics or features of the claimed invention, the specification implies that other characteristics or features are undesirable and should be excluded. Therefore, the court concluded that the exclusionary phrase was adequately described. Further, the Federal Circuit in *In re Wright* stated that the claimed subject matter need not be described "in haec verba." Based on *In re Wright*, applicants consider that the use of the exclusionary phrase in claim 32 of the present application is proper in light of the particular characteristics of the invention described below.

The claims of the present application are drawn to pharmaceutical compositions for the treatment of HPV infections and other serious pathologies such as cancer of the neck and of the uterus. Further, the goal of the present invention is to establish lasting immunity

against HPV and to limit the propagation of HPV infections. These features of the present invention require that HPV antigens, which will be effective prophylactically, be employed in the pharmaceutical compositions. Thus, it is contrary to the goals of the present invention and it would not be practical to use HPV antigens that are known to produce no prophylactic effects.

For example, an L2+E7 containing vaccine is detailed in WO93/00436 (Jarrett et al.) and WO94/23037 (Campo et al.) cited in the International Search Report and in the Information Disclosure Statement filed on March 12, 2001. The L2 and E7 polypeptides of BPV-4 were produced by a recombinant route in E. Coli as GST fusion proteins. An antitumoral protection of an immunoprophylactic type was observed in calves vaccinated with the mixture of purified GST-fused L2 + E7 polypeptides before the viral challenge (Figure 4 and Example 2 of WO 93/00436; Experiment #4 of Table 2, page 21 and Figure 3B of WO 94/23037). When comparing Figures 3 and 4 of WO 93/00436 and Figures 3B and 3C of WO 94/23037, one concludes that vaccination with either L2 or L2 +E7 results in the same prophylactic protective effect (in other words E7 is inefficient in this context). Moreover, in spite of the presence of E7 early polypeptide, the L2+E7 vaccine does not confer any protection against tumors pre-existing before the vaccination (therapeutic effect), as indicated in WO 93/00436 (page 15, last paragraph) and in WO 94/23037 (page 21, lines 22-25).

Further, it is interesting to note that recent data report the inefficiency of this L2+E7 formulation (Cantab Pharmaceutical's TH-GW human papillomavirus vaccine

comprising a mixture of L2 and E7 polypeptides of HPV-6 produced in E. coli) (submitted with the previous response dated March 12, 2001) and indicate that human clinical assays using the Cantab vaccine have been stopped due to its failure to demonstrate any therapeutic improvement over a placebo (see *Antiviral Agents Bulletin*, Vol. 13, enclosed herewith). This data as well as the publications discussed above establish that the L2/E7 combination is ineffective and undesirable and teach away from the claimed invention. Thus, in accordance with *In re Wright* and in view of the discussion above, the specification implies that the L2 and E7 combination is undesirable and should be excluded.

In light of the foregoing, the specification adequately describes the exclusionary language, particularly when the specification is read in light of contemporary knowledge in the field. Hence, the proviso phrase which was included in claim 32 is not new matter. Accordingly, the Examiner is respectfully requested to withdraw the rejection of claim 32 under 35 U.S.C. § 112, first paragraph.

Claims 32, 39 and 41 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the invention was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

Specifically, the Examiner has stated that the specification does not teach the structural elements that the chimeric or variant polypeptides must possess to ensure proper function to practice the invention. In order to expedite prosecution in the subject

application and not acquiesce to the Examiner's rejection, Applicants have amended claims 39 and 41 to no longer recite "a native, a chimeric or a variant papillomavirus."

Therefore, Applicants respectfully request withdrawal of the rejection of claims 32, 39 and 41 under 35 U.S.C. § 112, first paragraph.

## V. Rejection Under 35 C.F.R. § 102(a)

Claims 23, 24, 32-34, 39-45 and 52-56 have been rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Stanley et al. in WO 96/29091. Applicants respectfully traverse this rejection.

Applicants submit that Stanley et al. does not use recombinant vector(s) expressing papilloma polypeptide(s) in the absence of IL-12 to treat papillomavirus-induced lesions or tumors. Therefore, the composition as claimed in amended claim 32 and, by way of consequence, its dependent claims 33-43 are novel in view of Stanley et al. Further, amended claim 44 and its dependent claims, are also not anticipated by Stanley et al.

Applicants note that Stanley et al. (WO 96/29091) was published on September 26, 1996. However, the present application properly claims benefit of priority to French application number 96 09584 filed on July 30, 1996, which was prior to the publication date of WO 96/29091. The Examiner has acknowledged the claim for foreign priority as well as receipt of the certified copy of the priority document on the front of the Office Action Summary. Applicants provide herewith an English language translation of French

application number 96 09584. Accordingly, Stanley et al. cannot be properly used as prior art under 35 U.S.C. § 102(a).

Therefore, Applicants respectfully request withdrawal of the rejection of claims 23, 24, 32-34, 39-45 and 52-56 under 35 U.S.C. § 102(a).

## VI. Rejections Under 35 U.S.C. § 103(a)

Claims 35-38 and 46-49 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Stanley et al. as applied to claims 23, 24, 32-34, 39-45 and 52-56 above, and further in view of Boursnell et al. (WO 92/16636), Meyer et al., Galloway, Hines et al. and Gajewski. Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden by showing, first, that the cited prior art coupled with the general knowledge at the time of the invention must contain some suggestion or incentive to motivate a skilled artisan to modify or combine references. *See In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the Examiner must show that the modification or combination of prior art references must have a reasonable expectation of success (at the time of the invention). *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the Examiner must show that the cited or combined references teach each and every limitation of the claims. *See In re Zurko,* 111

F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); *In re Wilson,* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

As noted above, Stanley et al. (WO 96/29091) was published on September 26, 1996 and the present application properly claims benefit of priority to French application number 96 09584 filed on July 30, 1996, which was prior to the publication date of WO 96/29091. Therefore, Stanley et al. cannot be properly used as prior art under 35 U.S.C. §§ 102(a)/103(a).

However, Applicants submit that Stanley et al. discloses that IL-12 expression is active in HPV-induced lesions which are beginning to regress and therefore propose to treat HPV-infected patients with a polynucleotide encoding IL-12 to facilitate regression of their lesions. In order to enhance regression, Stanley et al. proposes to combine IL-12 treatment with a recombinant vector encoding at least one papillomavirus antigen or antigenic fragment thereof to boost immunity against HPV.

Applicants draw the Examiner's attention to the fact that Stanley et al. recognized that non IL-12 cytokines do not play any role in HPV-induced tumors regression as indicated on page 3, lines 13-14, of WO 96/29091. In particular, the experimental data clearly establish that IL-2 expression is quite different from IL-12 expression in the different categories of cervical biopsies analyzed in this study. Indeed, in marked contrast to IL-12, IL-2 transcripts were detected in normal cervix (table e), as well as in some of the non-regressing lesions (5/8 in table c, 2/7 in table b). Relying on these data, Stanley et al. does not provide sufficient guidance to suggest a reasonable expectation of success when

employing immunostimulatory polypeptides other than IL-12 (e.g. IL-2, IL-7, B7.1 and B7.2), to treat HPV-induced lesions. Hence, the skilled person would not be able to predict that non IL-12 cytokines are active in HPV-induced tumors regression. Therefore, the skilled person would not be motivated to associate such immunostimulatory molecules with HPV polypeptides to provide lasting immunity and limit the occurrence of HPV infections. Moreover, Stanley et al. does not teach or suggest a prophylactic vaccine to treat papillomavirus infections.

Boursnell et al. (WO 92/16636) teaches a recombinant virus vector expressing HPV-16 E6, HPV-16 E7, HPV-18 E6 and HPV E7 polypeptides for use as an immunotherapeutic or vaccine against HPV-induced diseases. The working example illustrates more specifically a vaccinia virus expressing the early E6 and E7 open reading frames of both HPV strains as a fused polypeptide (E6-E7).

Boursnell et al. does not disclose nor give any suggestion regarding a vector-based composition further encoding either a late HPV polypeptide and/or an immunostimulatory polypeptide.

Meyer et al. relates to an MVA genome and identifies the six major deletions that have occurred during the attenuation process of the wild-type vaccinia strain. Meyer et al. provides general knowledge on the MVA vector but does not disclose or even suggest expressing the HPV polypeptides and, optionally, immunostimulatory molecules as specified in the present claims.

Galloway et al. is a review of human papillomavirus vaccines. This document teaches that it should be feasible to develop prophylactic vaccines to prevent HPV infections using the LI and L2 capsid proteins or therapeutic vaccines to modulate the development or recurrence of disease based on the E6 and E7 oncoproteins or other viral proteins. Galloway et al. discusses preclinical studies that have been performed with either late papillomavirus polypeptide (see page 190, second column of Galloway et al.) or early papillomavirus polypeptide (see page 191, from the second sentence to the end of the first paragraph of the first column of Galloway et al.).

Applicants draw the Examiner's attention to the fact that all prophylactic vaccination studies were performed with late papillomavirus polypeptides recombinantly produced as fusion proteins. For example, Galloway et al. describes i) calves vaccinated with BPV 2 L1 or L2 fusion proteins that developed fibromas or fibropapilloma, respectively, which regressed rapidly postchallenge in comparison with unvaccinated calves; ii) similar results reported for another cutaneous BPV, BPV-1, and an L2 fusion protein from a mucosal virus (BPV-4) protected against challenge by BPV-4 via the palate; and iii) more recent studies showing that either L1 or L2 CRPV fusion proteins could confer immunity.

Therapeutic vaccination includes the use of papilloma early antigens produced from tumoral cell lines or recombinant viruses that have been injected into the host (Mice inoculated with fibroblasts expressing HPV-16 E6 or E7 could reject challenge by a melanoma cell line expressing the HPV oncogenes. Vaccinia virus recombinants

expressing the BPV E5, E6 or E7 genes could retard the development of tumors resulting from challenge with a BPV-transformed cell line in syngenic rats).

Galloway et al. further discloses at page 191, second column, that it is unclear "whether therapeutic vaccines should be based on early or late antigens or combination of these." The only combination which is disclosed in this document relies on an L2-E7 fusion protein (see paragraph bridging page 190 and 191). Injection of this combination formulation allowed the reduction, severity and duration of papillomavirus lesions. As discussed in our response to the previous Official Action, the L2+E7 containing vaccine is described in WO 93/00436 (Jarrett et al.) and WO 94/23037 (Campo et al.) cited in the international search report. The L2 and E7 polypeptides of BPV-4 are produced by recombinant route in E. coli as GST fusion proteins. An antitumoral protection of immunoprophylactic type is observed in calves vaccinated with the mixture of purified GST-fused L2 + E7 polypeptides before the viral challenge (Figure 4 and Example 2 of WO 93/00436 ; Experiment # 4 of Table 2, page 21 and Figure 3B of WO 94/23037). When comparing Figures 3 and 4 of WO 93/00436 and Figures 3B and 3C of WO 94/23037, one concludes that vaccination with either L2 or L2+E7 results in the same prophylactic protective effect (i.e., E7 is inefficient in this context). Moreover, in spite of the presence of E7 early polypeptide, the L2+E7 vaccine does not confer any protection against tumors preexisting before the vaccination (therapeutic effect), as indicated in WO 93/00436 (see page 15, last paragraph) and in WO 94/23037 (see page 21, lines 22-25).

As already mentioned to the Examiner, the human clinical assays using Cantab's TH-GW vaccine (based on an L2-E7 fusion protein) were stopped due to its failure to demonstrate any therapeutic improvement over a placebo (see Antiviral Agents Bulletin Vol 13, attached hereto).

In summary, Galloway et al. teaches a composition comprising:

- a recombinant vector expressing an early papillomavirus polypeptide(s) to treat HPV infections
- late papillomavirus fusion polypeptide(s) to prevent HPV infections, and
- a E7+L2 fusion protein.

Galloway et al. does not teach a composition relying on a recombinant vector to express either late or late and early HPV polypeptides. As a result, one skilled in the art would not be motivated to modify the composition of Galloway et al. to arrive at the present invention since it is unclear from the prior art whether other early and late HPV polypeptide combinations could provide effective protection or treatment against HPV-induced diseases. Moreover, Galloway et al. does not teach the action of immunostimulatory polypeptides to enhance the protective effect conferred by the papilloma polypeptides.

Hines et al. relates to recombinant papillomavirus-like particles used as prophylactic subunit vaccines to protect against naturally transmitted HPV infections. Beside this prophylactic aspect, Hines et al. discusses a cellular adoptive therapy protocol which relies on the administration of cytotoxic T lymphocytes. The naive lymphocytes obtained from a

host's peripheral blood lymphocytes or a histocompatible donor are *in vitro* stimulated with IL-2 and an HPV early peptide before being perfused into a cancer patient. Hines et al. states that "this modality involves obtaining peripheral blood lymphocytes from a cancer patient or a histocompatible donor. The lymphocytes are then stimulated with a peptide and cytokines *in vitro*. Once activated, the lymphocytes are returned to the cancer patient as therapy" (see page 862, second column, last paragraph, of Hines et al.).

Therefore, Hines et al. is primarily concerned with the use of (1) late Ll and L2 HPV polypeptides that have been produced and assembled *in vitro* in the form of virus-like particles and (2) a lymphocyte composition previously *in vitro* activated by the action of IL-2 and an HPV early peptide (i.e., a cellular composition). However, Hines et al. does not teach injecting into a patient IL-2 together with HPV polypeptide(s) to enhance the therapeutic effect of the latter. As a result, the skilled artisan would not be motivated to utilize recombinant vector(s) expressing IL-2 and one or more HPV polypeptide(s) to obtain immunity against HPV infections.

Gajewski relates to B7.1-induced stimulation of naive lymphocytes to cytotoxic T lymphocytes (CTLs). To this end, the B7.1 cDNA was transfected into P815 mastocytoma cells. Mouse splenocytes were then stimulated with the transfected cells in the presence of an anti-CD3 antibody. B7.1 transfected tumor cells stimulated proliferation of CD4+ as well as CD8+ T cells. As discussed on page 470 of Gajewski, direct co-stimulation of CD8+ T lymphocytes by expression of B7.1 allows the emergence of CTLs that produce their own IL-2. It is suggested that expression of B7.1 on human tumor cells can render

them better able to stimulate CD8+ lymphocytes and that utilization of B7.1-expressing autologous tumor cells may provide a plausible immunization approach for cancer patients.

Thus, Gajewski is not relevant to the instant invention as it is primarily directed towards the use of a cellular composition comprising B7.1 transfected tumor cells to treat a cancer patient. Gajewski does not mention or suggest injecting B7.1 together with a (HPV) polypeptide to provide protection against a viral (HPV) infection. At best, Gajewski merely provides the person skilled in the art with the suggestion to modify the stimulation protocol disclosed by Hines et al. and to perform the *in vitro* stimulation of the naive lymphocytes with B7.1 rather than with IL-2.

In conclusion, the references cited by the Examiner, singly or in combination, do not render obvious the newly amended claims 32-43 drawn to a composition combining at least one early and one late HPV polypeptides with the exception of the specific L2+E7 combination. Starting with Galloway et al., which teaches a polypeptide-based L2+E7 composition, the skilled person would not be motivated to practice other early and late combinations in view of the inefficiency of the specific L2+E7 combination (compared to a L2 composition as reported in WO 93/00436 and WO 94/23037) and the uncertainty mentioned in this document (i.e., it is unclear "whether therapeutic vaccines should be based on early or late antigens or combination of these."). The deficiencies of this document are not cured by the other cited references.

With respect to amended claims 44 and 46-52 reciting a vector-based composition expressing an HPV polypeptide and an immunostimulatory polypeptide, the references cited

by the Examiner do not render these claims obvious because Galloway et al. fails to teach the action of the immunostimulatory polypeptide to enhance the protective effect conferred by the papilloma polypeptides and this deficiency is not cured by the *in vitro* stimulated cellular composition disclosed in Hines et al. and Gajewski. Furthermore, in view of the statement in Stanley et al. regarding the functional difference existing between IL-12 and the other cytokines (i.e., IL-12 is present in 100% of regressing HPV-induced tumors, surveyed by the present inventors in a clinical study-unlike many other cytokines also surveyed) (page 3, lines 11-14, of Stanley et al.), the skilled person would not be able to predict the therapeutic effect provided by the non-IL-12 cytokines in the treatment of HPV-induced lesions and, hence, would not be motivated to utilize the non-IL-12 cytokines to enhance regression of HPV-induced tumors. The same argument applies to the vector composition expressing a (early or late) papillomavirus polypeptide and an immunostimulatory molecule as recited in newly added claims 65-81.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 35-38 and 46-49 under 35 U.S.C. § 103(a).

Claims 50 and 51 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Stanley et al., Boursnell et al., Galloway, Hines et al., Gajewski and Meyer et al. as applied to claims 32-49 and 52-56 above, and further in view of Crook et al. and Munger et al.

As already discussed above, the reference of Stanley et al. is not proper art under 35 U.S.C. §§ 102(a)/103(a). Further, as discussed above, the combination of Stanley et al.,

Boursnell et al, Galloway et al., Hines et al., and Gajewski do not render the claimed invention obvious. Accordingly, Munger et al. and Crook et al. in combination with Stanley et al., Boursnell et al., Galloway et al., Hines et al., and Gajewski also do not render the claimed invention obvious.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 50 and 51 under 35 U.S.C. § 103(a).

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Teresa Stanek Rea
Registration No. 30,427

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: September 24, 2001

**Attachment to Amendment dated September 24, 2001**
**Marked-up Claims**

32. (Amended) A composition comprising one or more recombinant vectors into which are inserted (i) at least one DNA sequence coding for an early polypeptide of a papillomavirus and (ii) at least one DNA sequence coding for a late polypeptide of a papillomavirus, with the exception of the specific combination of DNA sequence coding for the E7 early polypeptide and of DNA sequence coding for the L2 late polypeptide of human papillomavirus; said DNA sequences being placed under the control of the elements necessary for their expression in a host cell or organism and wherein said composition does not comprise one or more recombinant vectors into which are inserted DNA sequences coding for at least one polypeptide having an immunostimulatory activity.

39. (Amended) The composition of claim 32, wherein said early polypeptide is [selected from a native, a chimeric or a variant papillomavirus] E6 [and/or] or the E7 or the E6 and E7 polypeptide of a papillomavirus .

40. (Amended) The composition of claim [39] 32, wherein said early polypeptide is a nononcogenic E6 and/or E7 polypeptide of a papillomavirus.

41. The composition of claim 32, wherein said late polypeptide is [selected from a native, a chimeric or a variant papillomavirus] L1 [and/or] or the L2 or the L1 and L2 polypeptide of a papillomavirus

42. (Amended) The composition of claim 32, wherein said DNA sequences encode the early E6 and E7 polypeptide and the late [polypeptide] L1 and L2 polypeptide of a papillomavirus.

44. (Amended) [The] A composition [of claim 32] comprising one or more recombinant vectors into which are inserted (i) at least one DNA sequence coding for an early polypeptide of a papillomavirus and (ii) at least one DNA sequence coding fro a late polypeptide of a papillomavirus, with the exception of the specific combination of DNA sequence coding for te E7 early polypeptide and DNA sequence coding for the L2 late polypeptide of human papillomavirus; said DNA sequences being placed under the control of the elements necessary for their expression in a host cell or organism and further comprising one or more recombinant vectors into which are inserted DNA sequences coding for [At] at least one polypeptide having an immunostimulatory activity wherein said DNA sequences are placed under the control of the elements necessary for their expression in a host cell or organism and wherein said polypeptide having an immunostimulatory activity is selected from the group consisting of interleukin-2, interleukin-7, the co-adhesion molecule B7.1 and the co-adhesion molecule B7.2.

46. (Amended) The composition of claim 44, wherein the polypeptide having an immunostimulatory activity is [interleukine-2] interleukin-2.

48. (Amended) The composition of claim 44, comprising one or more recombinant vectors into which are inserted :

(a) a DNA sequence coding for the E6 polypeptide of a papillomavirus, a DNA sequence coding for the E7 polypeptide of a papillomavirus, a DNA sequence coding for the L1 polypeptide of a papillomavirus, a DNA sequence coding for the L2 polypeptide of a papillomavirus and a DNA sequence coding for the co-adhesion molecule B7.1, or

(b) a DNA sequence coding for the E6 polypeptide of a papillomavirus, a DNA sequence coding for the E7 polypeptide of a papillomavirus, a DNA sequence coding for the L1 polypeptide of a papillomavirus, a DNA sequence coding for the L2 polypeptide of a papillomavirus and a DNA sequence coding for [interleukine-2] interleukin-2, or

(c) a DNA sequence coding for the E6 polypeptide of a papillomavirus, a DNA sequence coding for the E7 polypeptide of a papillomavirus, a DNA sequence coding for the LI polypeptide of a papillomavirus, a DNA sequence coding for the L2 polypeptide of a papillomavirus, a DNA sequence coding for the co-adhesion molecule B7.1 and a DNA sequence coding for [interleukine-2] interleukin-2.

52. (Amended) The composition of claim 44, further comprising [in] a pharmaceutically acceptable carrier.

#10
Attach
09/506,942

# EXHIBIT A

## *TH-GW Human Papillomavirus Vaccine Development Halted by Cantab and SKB.*

Date : 20001000

Sous-titre :

Development for Cantab Pharmaceuticals Plc's TH-GW genital wart vaccine has been ceased due to lack of success in Phase II trials.

Source article :

Antiviral Agents Bulletin; Volume: 13; Issue: 10; Page: N/A; October 2000; ISSN: 0897 9871; United States.

Société : CANTAB PHARMACEUTICALS PLC; SMITHKLINE BEECHAM BIOLOGICALS; <SMITHKLINE BEECHAM PLC>

Résumé :

Cantab Pharmaceuticals plc (Cambridge, U.K.) and its development collaborator, SmithKline Beecham Biologicals (SKB; Rixensart, Belgium), have announced discontinuation of development of Cantab's TH-GW immunotherapeutic human papillomavirus (HPV) vaccine for treatment of genital warts after the vaccine failed to show efficacy in the first of two Phase II trials. TH-GW is a subunit fusion protein vaccine formulated from two fused HPV-6 proteins (L2 and E7) expressed in E. coli along with a proprietary adjuvant (SBAS2 from SKB) to increase T lymphocyte response. The SBAS2 adjuvant is based on the combination of monophosphoryl lipid A (MPL), a detoxified form of Lipid A lipopolysaccharide purified from Salmonella minnesota R595 bacteria, from Corixa Corp. (originally Ribi ImmunoChem), combined with QS21 (QS-21), a purified fraction of saponin extracted from Quillaja saponaria, from Aquila Biopharmaceuticals, Inc. (originally Cambridge Biotech Corp.), plus a proprietary oil-in-water emulsion. The original agreement between Cantab and SKB for development of TH-GW was reported in the July 1996 Bulletin (p. 170). An earlier Phase IIa trial had shown the vaccine to have promise for treatment of genital warts, as reported in the December 1996 Bulletin (p. 324). In the recently completed Phase II trial, no significant difference in the recurrence rate for genital warts was observed at six months between patients receiving TH-GW and a placebo. The trial had enrolled genital warts patients having failed other therapies. The stock price of Cantab in the U.K and U.S. (NASDAQ) declined about 60% shortly after the announcement. However, Cantab has other HPV vaccines in development. TA-CIN is currently in Phase I trials for treatment of cervical dysplasia (as discussed in the July Bulletin, p. 202). TA-CIN is a recombinant HPV type 16 fusion protein which has shown encouraging therapeutic and prophylactic effects in animal models. TA-HPV is in Phase II trials for treatment of cervical

cancer. TA-HPV uses a recombinant vaccinia virus vector for intracellular expression of HPV E6 and E7 antigens which stimulate cytotoxic T lymphocyte (CTL) immunity. This vaccine has shown indications of efficacy as reported in the December 1997 Bulletin (p. 364). Other products in development by Cantab include a DISC HSV vaccine. As reported in the August Bulletin (p. 229), Cantab recently regained rights to this vaccine for prophylactic use from Glaxo Wellcome plc as a result of Glaxo Wellcome's upcoming merger with SKB.



THIS IS A LEAD PARAGRAPH; FULL TEXT IS AVAILABLE IN FORMATS 'LONG' & 'ALL'.

Texte :

Cantab Pharmaceuticals plc (Cambridge, U.K.) and its development collaborator, SmithKline Beecham Biologicals (SKB; Rixensart, Belgium), have announced discontinuation of development of Cantab's TH-GW immunotherapeutic human papillomavirus (HPV) vaccine for treatment of genital warts after the vaccine failed to show efficacy in the first of two Phase II trials. TH-GW is a subunit fusion protein vaccine formulated from two fused HPV-6 proteins (L2 and E7) expressed in E. coli along with a proprietary adjuvant (SBAS2 from SKB) to increase T lymphocyte response. The SBAS2 adjuvant is based on the combination of monophosphoryl lipid A (MPL), a detoxified form of Lipid A lipopolysaccharide purified from Salmonella minnesota R595 bacteria, from Corixa Corp. (originally Ribi ImmunoChem), combined with QS21 (QS-21), a purified fraction of saponin extracted from Quillaja saponaria, from Aquila Biopharmaceuticals, Inc. (originally Cambridge Biotech Corp.), plus a proprietary oil-in-water emulsion. The original agreement between Cantab and SKB for development of TH-GW was reported in the July 1996 Bulletin (p. 170). An earlier Phase IIa trial had shown the vaccine to have promise for treatment of genital warts, as reported in the December 1996 Bulletin (p. 324). In the recently completed Phase II trial, no significant difference in the recurrence rate for genital warts was observed at six months between patients receiving TH-GW and a placebo. The trial had enrolled genital warts patients having failed other therapies. The stock price of Cantab in the U.K and U.S. (NASDAQ) declined about 60% shortly after the announcement. However, Cantab has other HPV vaccines in development. TA-CIN is currently in Phase I trials for treatment of cervical dysplasia (as discussed in the July Bulletin, p. 202). TA-CIN is a recombinant HPV type 16 fusion protein which has shown encouraging therapeutic and prophylactic effects in animal models. TA-HPV is in Phase II trials for treatment of cervical cancer. TA-HPV uses a recombinant vaccinia virus vector for intracellular expression of HPV E6 and E7 antigens which stimulate cytotoxic T lymphocyte (CTL) immunity. This vaccine has shown indications of efficacy as reported in the December 1997 Bulletin (p. 364). Other products in development by Cantab include a DISC HSV vaccine. As reported in the August Bulletin (p. 229), Cantab recently regained rights to this vaccine for prophylactic use from Glaxo Wellcome plc as a result of Glaxo Wellcome's upcoming merger with SKB.



THIS IS THE FULLTEXT.